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PRE-APPEAL BRIEF REQUEST FOR REVIEW

Docket Number (Optional): SHE 0037.14 / 41714-8011.US03

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Typed or printed name Deneene Mariscal

Application Number	Filed
10/647,561	August 25, 2003

First Named Inventor: Bentley

Art Unit	Examiner
1654	Heard, Thomas Sweeney

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

- ☐ applicant/inventor.
- ☐ assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)
- ☑ attorney or agent of record. Registration number 38,443
- ☐ attorney or agent acting under 37 CFR 1.34. Registration number if acting under 37 CFR 1.34 _____

Susan T. Evans
Signature

Susan T. Evans
Typed or printed name

650-590-1918
Telephone number

August 28, 2008
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☐ *Total of _____ forms are submitted.

This collection of information is required by 35 U.S.C. 132. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11, 1.14 and 41.6. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: Michael David Bentley, *et al.*	EXAMINER: Thomas Sweeney Heard
APPLICATION NO.: 10/647,561	ART UNIT: 1654
FILED: August 25, 2003	CONF. NO: 3230
FOR: **POLYMER STABILIZED NEUROPEPTIDES**	

Pre-Appeal Brief Request for Review

Mail Stop AF
Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

Sir:

This request is for a Pre-Appeal Brief conference by a panel of Examiners to review the outstanding rejection in the above identified application as stated in a Final Office Action dated May 28, 2008. This request is accompanied by a Notice of Appeal, and contains no amendments, affidavits or other evidence. The claims under consideration are those resulting from Applicant's Amendment under 37 C.F.R. 1.111 filed on February 15, 2008.

I. Status of Claims:

Claims 1-3, 6-16, 18, 19, 23, 24, 26, and 27 are pending (contrary to Office Action Summary).

Claims 4, 5, 17, 20-22, and 25 are canceled.

Claim 24 is currently withdrawn as being directed to a non-elected specie; the specie was elected for initial search purposes only.

II. Outstanding Rejection

Claims 1-3, 6-19, 23, 26 and 27 stand as finally rejected under 35 U.S.C. § 103(a) as unpatentable over the combination of Delgado et al., Wu et al., and Sakane et al., *Pharmaceutical Research*, 1997, vol. 4(8), 1085-1091 (Sakane)[1].

[1] In the current final Office Action, the Examiner states that the prior rejection of claims 1-3, 5-19, 21, 23, and 27 under 35 U.S.C. §103(a) as unpatentable over Delgado and Wu has been overcome in light of Applicant's amendment to the claims. (The claims were amended to recite a conjugate that "consists of" rather than "comprises" certain features). In view of the foregoing, the Examiner must therefore be relying on Sakane to make up the deficiencies of Delgado and Wu in the current and only remaining rejection.

Reconsideration of this rejection is respectfully requested. Applicant submits that the Examiner has failed to meet the requirements for establishing a *prima facie* case of obviousness.

III. Representative Claims

The claims are directed to a hydrophilic polymer-peptide conjugate, *consisting of:*

(i) a peptide that is either biphalin or [D-Pen2, D-Pen5]enkephalin (DPDPE),

(ii) covalently linked to one or more water-soluble polymer chains having a molecular weight from about 2,000 to about 100,000 daltons and selected from either poly(ethylene glycol) or copolymers of ethylene glycol and propylene glycol,

which

(iii) when administered into the blood circulation of a mammal, is capable of transport across the blood brain barrier (BBB).

It is the combination of features (i) -(iii) that is unexpected and surprising in view of the art relied upon by the Examiner.

IV. Brief Characterization of the Art

Delgado, et al. and Wu et al. have been previously characterized in Applicant's prior Amendments (See, e.g., Applicant's Amendment of November 17, 2006, pages 6-8, and Applicant's Amendment dated April 5, 2007, pages 8-10).

Sakane et al. is newly cited by the Examiner. Sakane describes methods for carboxyl-directed PEGylation of brain-derived neurotrophic factor (BDNF) to improve its pharmacokinetic profile and reduce systemic clearance without adversely affecting the protein's biologic activity (as reportedly occurs with modification of surface lysine residues of nerve growth factor-like neurotrophins).

Although Sakane does indeed describe that the pharmacokinetic profile of BDNF is improved by carboxyl-directed conjugation with relatively large PEG-2000 and PEG-5000, this point is absolutely irrelevant to an analysis of the claims at hand. More important to the instant analysis, Sakane shows that (i) the brain volume of distribution of BDNF is progressively decreased following PEGylation with either PEG-2000 or PEG-5000, and further that (ii) the organ volume of distribution of BDNF-PEG^{5000} was not significantly different from the brain

plasma volume (see page 1087, 2nd column)[2]. Thus, Sakane observed no significant transport of the prepared BDNF-PEG conjugates across the BBB - a point completely ignored by the Examiner in his assertion of a "reasonable expectation of success in producing the claimed invention" (Final Office Action, page 6, final paragraph).

Further, Sakane suggests that PEGylated BDNF as described in that reference can be further modified and attached to an MAb/avidin delivery system to facilitate neuropeptide delivery through the BBB (page 1090, 2nd column, last paragraph preceding Acknowledgements). Thus, Sakane is actually *teaching away* from the Applicant's claims by suggesting that if transport across the BBB is desired for the subject conjugates, one must further modify the PEG to attach a biotin moiety, which may then be attached to an MAb/avidin delivery system. Such an approach clearly falls outside of the Applicant's claims.

V. Examiner's Failure to Establish a Prima Facie Case of Obviousness - Argument

As reiterated by the Supreme Court *in KSR International Co. v. Teleflex, Inc.*, 82 USPQ2d 1385, 1391 (2007), the framework for making an objective determination of obviousness is that stated in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966) (MPEP, Section 2141 and current Office action, page 3). As part of this analysis, both the claims and the prior art must be considered *as a whole*, including portions that would lead away from the claimed invention.

The Applicant submits that there is nothing in the art relied upon by the Examiner to prompt one of skill in the art in the relevant field to combine or modify the elements in the way the claimed invention does. Indeed, in the instant rejection, it is submitted that the Examiner has ignored the unpredictable nature of the instant claims in view of the art of record teaching away from the same, and has failed to consider the claims *as a whole*. In view of the foregoing, a *prima facie* case of obviousness cannot be made.

The following remarks are in support of a clear deficiency in the prima facie case:

Delgado is a review article describing various PEGylated proteins and their pharmacological properties, including methods of synthesis and analysis. Delgado has nothing to do with small peptides such as biphalin ((Try-D-Ala-Gly-Phe-$NH)_2$) or DPDPE (Tyr-D-Pen-Gly-Phe-D-Pen), and is completely silent regarding the impact of PEGylation with relatively large polymers on the ability of any compound, let alone a small peptide such as biphalin or DPDPE, to cross the BBB.

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[2] An apparent brain volume of distribution above the plasma volume is interpreted as evidence for BBB transport

Wu et al. describe the modification of brain-derived neurotrophic factor (BDNF, a 27.0 kDa protein) to improve its pharmacokinetic properties and to enable crossing of the BBB. Specifically, Wu states that conjugation of PEGylated BDNF to an OX26 Mab BBB transport vector *is required* to allow transport of the protein across the BBB (Abstract). Wu stresses that for a neurofactor to have therapeutic utility, it is a requirement that the protein be modified to both improve its plasma pharmacokinetic properties and to enable crossing of the BBB by coupling to a transport vector such as OX26 Mab. For example, Wu states in the final paragraph on page 258, "[t]he results of the present investigation indicate that if the neurotrophic factor undergoes a defined molecular reformulation, such as that depicted in Fig. 1, both to enable BBB transport and to optimize plasma pharmacokinetics, then these molecules may have therapeutic effects in the brain after peripheral administration." (emphasis added). When viewed as a whole, it is clear that Wu teaches that a therapeutic neuroprotein must be conjugated to a transport vector to allow crossing of the BBB in order for the active agent to have therapeutic utility.

Thus, the subject matter of the Applicant's claims, which recite a conjugate *consisting of* a peptide that is either biphalin or [D-Pen2, D-Pen5]enkephalin (DPDPE), covalently linked to one or more relatively large water-soluble PEG or PEG-PPG polymer chains, which (iii) when administered into the blood circulation of a mammal, is capable of transport across the blood brain barrier (BBB) - is absolutely unpredictable in view of the teachings of Wu et al. In no way can the modification of the teachings of Wu, to omit an element (i.e., the transport vector portion) stated by Wu to be critical to transport across the BBB, be considered a predictable modification of the art.

Further to this point, Sakane, consistent with the teachings of Wu et al., teaches that to impart the ability of the PEGylated BDNF to cross the BBB, the PEGylated BDNF should be further conjugated to a transport vector. See, e.g., page 1085, last sentence of 1st column, and page 1090, 2nd col., last paragraph, which states "[t]hus, the pegylated BDNF may then be attached to a MAb/avidin delivery system, which has been used in previous studies to facilitate neuropeptide delivery through the BBB (5). These results suggest that neurotrophins may be converted into more effective neuropharmaceuticals through drug delivery strategies that place importance on the dual task of optimizing both plasma pharmacokinetics, (with the use of pegylation technology), and transcellular membrane transport, (with the use of vector-mediated drug delivery systems)." (emphasis added)

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across the BBB (Sakane, page 1090, column 1).

Indeed, when considering the reference as a whole, Sakane demonstrates that the brain volume distribution of BDNF is decreased upon PEGylation, and that BDNF or other neuroproteins that do not cross the BBB *must be* coupled to an agent or delivery system that enables BBB transport to produce therapeutic efficacy. Thus, the art relied upon provides absolutely no reason for one of skill in the art to combine/modify the elements in the way the claimed invention does to achieve a conjugate capable of transport across the BBB.

Finally, the art relied upon by the Examiner is directed to large proteins such as BDNF rather than small neuropeptides of the type claimed. When considered as a whole, it is submitted that Examiner has not given fair consideration to the surprising and unpredictable finding that small neuropeptides, such as biphalin and DPDPE, conjugated to large hydrophilic PEG polymers retain their biological activity and are able to cross the BBB. See, e.g., Applicant's specification, which demonstrates: (i) biphalin and DPDPE conjugated to relatively large PEG are able to cross the BBB barrier and produce an analgesic effect *in vivo* after intravenous injection in mice (paragraphs [0094] to [0097] on pages 22 and 23 and Figures 2-6); (ii) PEG-DPDPE produces an analgesic effect (Figure 2 and paragraph [0094]), (iii) PEGylation of DPDE significantly prolongs the duration of analgesic effect; (iv) all PEGylated biphalin exhibited a potent analgesic response in mice, with a maximum response of 80-90% M.P.E. reached between 30-45 minutes (paragraph [0095]).

For the foregoing reasons, it is submitted that compounds having the features recited in the instant claims, PEGylated biphalin or DPDPE, having the ability to cross the BBB in sufficient amounts to produce an analgesic effect, are surprising and unexpected in view of the art of record.

In view of the above, Applicant submits that there is clear deficiency in the prima facie case. Withdrawal of the outstanding rejection under 35 U.S.C. § 103(a) and a favorable decision on the allowability of the pending claims is respectfully requested.

Respectfully submitted,
King & Spalding LLP

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August 28, 2008

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